Bandolier 108

Independent evidence-based health care

All about aspirin

Low dose (75 mg) aspirin prescribing rose rapidly in the 1990s [1], as fast as that for proton pump inhibitors (Figure 1). The same paper tells us that hospital admissions for gastric and peptic ulcer rose by about 10-30% in 65-74s and 30-40% in over 75s. For duodenal ulcer, finished consultant episodes rose by 25% for men and women aged 65-74 years, and 30-50% for men and women over 75 years or over. It wasn't due to increased NSAID prescribing (Figure 1), and rocketing PPI consumption should have helped prevent these problems.

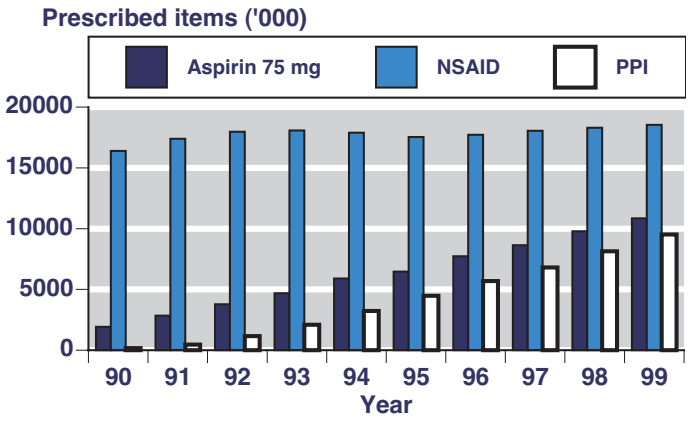
Were the GI problems all down to aspirin? If each prescription was for 30 tablets (a conservative assumption) and one 75 mg tablet was taken a day, then by 1999 there would have been 900,000 more person years of exposure. Given that one or two gastrointestinal bleeds per 1000 patients on low dose aspirin, then low dose aspirin could account for 1000 to 2000 episodes of gastrointestinal bleeding, and that approximates the 1000 excess admissions actually observed.

We need to know that we are not doing more harm than good. This issue of ***Bandolier*** reviews the excellent evidence that that is so when the annual risk of a coronary event is about 1% or greater. For secondary prevention, low dose aspirin makes excellent sense, with nothing else much better. But aspirin does not beat anticoagulants for preventing stroke in nonvalvular atrial fibrillation.

Reference:

1 J Higham et al. Recent trends in admissions and mortality due to peptic ulcer in England: increasing frequency of haemorrhage among older subjects. Gut 2002 50: 460-464.

Figure 1: Prescribing of aspirin, NSAIDs and proton pump inhibitors (PPI) in England



Aspirin in high risk patients

Most of us are content that aspirin is effective in reducing vascular events in people at high risk, and while not every candidate patient receives aspirin, every year more of them do. Much of the impetus has come from impressive meta-analyses showing solid evidence of efficacy. Reinforcement in the form of an updated meta-analysis with many more patients in randomised trials is a welcome addition [1]. No précis can do justice to the detail of a paper that takes 16 pages of the BMJ plus more available electronically, but the main results carry the message.

Meta-analysis

All relevant trials available up to September 1997 were sought through an intensive search strategy of electronic databases, trial registers, manual searching, reference lists and inquiry to researchers and pharmaceutical companies. Trials had to compare an antiplatelet regimen with control or with another antiplatelet regimen in patients at high annual risk (over 3% a year). Trials had to be properly randomised.

The outcome was one of preventing "all bad things happening", in this case defined as a serious vascular event (non-fatal myocardial infarction, non-fatal stroke, or death). Individual trialists were asked about details of randomisation, blinding, duration of treatment and follow up, and those with at least 200 randomised patients were asked for information on individual patients (age, sex, blood pressure, medical history) and outcomes in individual patients.

Deaths were divided into those with a vascular cause (cardiac, cerebrovascular etc) and those that were definitely non-vascular. Strokes were subdivided into intracranial haemorrhage and those that were ischaemic or of unknown cause. Major extracranial bleeds were also considered an endpoint, and the definition of serious was applied for those needing hospital admission or blood transfusion.

In this issue

Table 1: Results in particular high risk groups, antiplatelet versus control

Condition	Number of trials	Number (%) vascular events		Percent odds reduction	Benefit/1000 patients	Mean months of treatment
		Antiplatelet	Control			
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10022 (17.0)	25	36	27
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	30	38	1.0
Previous stroke, TIA	21	2045/11493 (17.8)	2464/11527 (21.4)	22	36	29
Other high risk	140	1638/20359 (8.0)	2102/20543 (10.2)	26	22	22
All high risk	188	6035/51494 (11.7)	7644/51736 (14.8)	25		
Acute stroke	7	1670/20418 (8.2)	1858/20403 (9.1)	11	9	0.7
All trials	**195**	**7705/71912 (10.7)**	**9502/72139 (13.2)**	**22**		

Table 2: Benefit or harm per 1000 patients in particular high risk groups, antiplatelet versus control

Condition	Mean treatment months	Benefit or harm/1000 patients				
		Non-fatal reinfarction	Non-fatal stroke	Vascular death	Any death	Fatal and non-fatal major extracranial bleeds
Previous myocardial infarction	24	18	5	14	12	**0**
Acute myocardial infarction	1	13	2	23	24	**0**
Previous stroke, TIA	36	6	25	7	15	**5**
Acute stroke	0.7	no data	4	5	5	**4**
Other high risk	no data	no data	no data	no data	no data	**9**

Table 3: Antiplatelet versus control, particular drugs and doses

Drug and dose (mg)	Number of trials	Percent vascular events		Percent odds reduction
		Antiplatelet	Control	
Aspirin 500-1500	34	14.5	17.2	19
Aspirin 160-325	19	11.5	14.8	26
Aspirin 75-150	12	10.9	15.2	32
Aspirin <75	3	17.3	19.4	13
Any aspirin	**65**	**12.9**	**16.0**	**23**
Dipyridamole	15	14.5	16.8	16
Dipyridamole + aspirin	46	10.7	14.3	30
Ticlopidine	42	8.1	11.1	32

Results

There were 195 trials with information on vascular events (135,000 patients) that compared antiplatelet with control, and 89 (77,000 patients) that compared different antiplatelet regimens. There were 7,705 serious vascular events (10.7%) in 71,912 patients with antiplatelet therapy and 9,502 (13.2%) in 72,139 with control.

The analysis provides results in various combinations, for instance combining all doses of all antiplatelets used for any duration above one day for particular conditions. When analysing particular antiplatelets against control, only aspirin doses are given separately. Numbers needed to treat were not calculated, nor odds ratios. Rather results are given in terms of benefit or harm for 1,000 patients treated together with the percentage reduction in odds of an event.

Particular high risk groups

The results for the five main categories of high risk patients are shown in Table 1 for the outcome of any vascular event. There was a consistent reduction in odds of any vascular event of about 20-30%, except for treatment of acute stroke with a mean of only three weeks of treatment. In all other high risk categories the benefit per 1,000 patients was 20-40, over one month for treatment of acute myocardial infarction, and over 22-29 months for other conditions.

Table 2 breaks down these into more detail, showing the particular vascular events avoided, together with all-cause death avoided. Benefit has to be balanced against risk of harm, the major risk being major extracranial bleeds. Treatment of acute myocardial infarction with antiplatelet for one month entailed considerable benefit in terms of vascular death or non-fatal reinfarction over one month. Treatment of previous stroke for three years avoided additional non-fatal strokes, but at the cost of some extracranial bleeds.

Particular antiplatelets

Dose and target patients complicate indirect comparison. The main results for the main antiplatelets are shown in Table 3. Again, there is a reasonably consistent pattern of event rates and degree of odds reduction. Aspirin 75-150 mg a day appears to be as effective as any other dose, and no other antiplatelet had spectacularly better effect.

Antiplatelet trials have often used aspirin as a comparison, though none of the comparisons has demonstrated spectacularly better results than aspirin alone (Table 4).

Comment

This paper is a "must-read" for those delivering antiplatelet therapy. And not just the abstract. Although it is a meta-analysis, and people are often mightily turned off with the prospect of wading though one of those, this paper is easily understandable by a reader without special knowledge.

There's something Shakespearean about it, with the main theme that antiplatelets work, but with a myriad subplots, from loading doses of aspirin after a heart attack, to the reasoning of a useful effect of antiplatelets in diabetics, even though the evidence for an effect in diabetes is weak. So whether your interest is atrial fibrillation in your granny, or cardiac valve surgery in a neighbour, you could answer the question about antiplatelets.

But one word of caution. The pooling of different doses is a potential problem. For instance, out of 65 comparisons of aspirin against control, only 12 (with 10% of the patients) were of the 75-150 mg doses commonly used in the UK. The problem is only averted by the consistency of results over different doses of different antiplatelets in many different conditions. That won't be the case in other meta-analyses, and in those, and here for very specific questions, other analyses will need to be done.

Aspirin or clopidogrel?

This question has also been the subject of review [2]. The bottom line was that clopidogrel and ticlopidine prevent a few more vascular events than aspirin (NNT 92), at a cost of somewhat more adverse events. The implications for costs are significant. Treating 1000 patients with clopidogrel rather than aspirin could prevent as many as 19 vascular events at a cost of £57,000 ($85,000) per event prevented, or as few as two events at a cost of £533,000 ($800,000) per event prevented. The evidence is abstracted in more detail on the Bandolier internet site.

References:
1 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002 324: 71-86.
2 GJ Hankey et al. Thienopyridines or aspirin to prevent stroke and other serious vascular events in patients at high risk of vascular disease? A systematic review of the evidence from randomized trials. Stroke 2000 31: 1779-1784.

Table 4: Antiplatelet regiments versus aspirin alone

Antiplatelet or combination	Number of trials	Percent vascular events		Percent odds reduction
		Antiplatelet regimen	Aspirin	
Aspirin + dipyridamole	25	11.8	12.4	6
Dipyridamole	3	16.7	16.5	-2
Ticlopidine	4	21.1	23.2	12
Clopidogrel	1	10.1	11.1	10

Secondary prevention with aspirin

The Antithrombotic Trialists' Collaboration was a remarkable tour de force. The trouble some would see is that in combining 195 trials with different antithrombotics in different patients for different times the analysis misses the main point: that of convincing physicians to prescribe aspirin in low doses for secondary prevention.

This has been addressed in a different analysis [1]. Here the essence was to find trials that informed on the FDA-approved uses of low dose (50-325 mg/day) aspirin. These are in the secondary prevention of myocardial infarction and stroke in patients with previous infarction, stroke or transient ischaemic attack, or those patients with a history of angina.

Systematic review

Searching used electronic databases for all published reports since 1970 that informed on the FDA's updated professional labelling for aspirin. For inclusion, studies had to be randomised, with a placebo control, and use aspirin at doses of 50-325 mg/day. Excluded were trials of duration shorter than three months, trials that used short-term prophylaxis in procedures (like angioplasty or bypass surgery), trials that combined aspirin with another agent or used aspirin in otherwise healthy individuals.

Outcome data collected included myocardial infarction, stroke, vascular death, vascular events (any stroke, myocardial infarction or vascular death), and all cause mortality. Gastrointestinal bleeding events were included regardless of severity.

Results

There were six trials with 6,300 patients; about 4,200 had had a myocardial infarction or stroke. Subjects were predominantly men, with mean age in trials of mid-50s to mid-60s. Duration of studies appeared to be from three to 52 months.

All six trials had fewer deaths with aspirin than with control. There were significantly fewer deaths, combined vascular events, and myocardial infarctions, but more gastrointestinal bleeds (Table 1). Of the 41 gastrointestinal bleeds with aspirin 24 were severe, and of the 17 bleeds with placebo 9 were severe. No deaths were caused by bleeding.

Benefits outweighed risks (Figure 1). The results indicated that if 1000 patients were treated with aspirin prophylactically as secondary prevention instead of not being treated, there would be 55 fewer vascular events (including 27 myocardial infarctions and 11 strokes), and 15 fewer deaths. Off set against this benefit would be 8 more episodes of bleeding, of which about half would be severe.

Comment

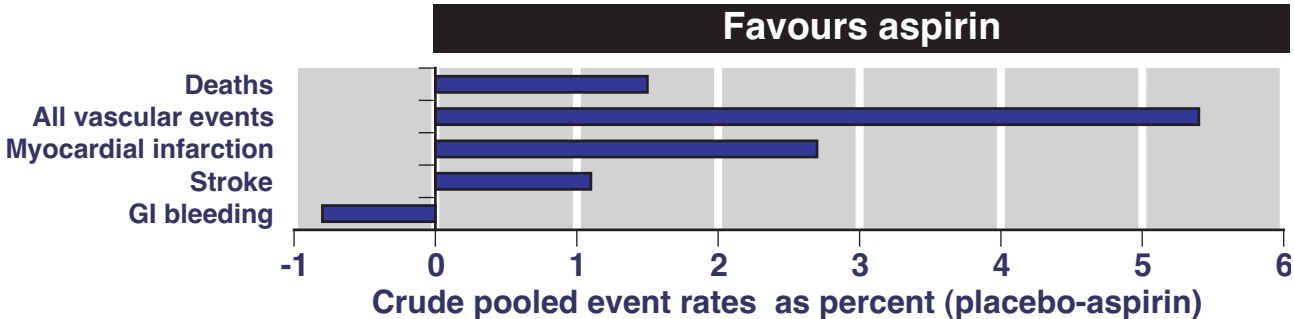
This is reassuring information for those who want to know that aspirin is effective and safe not across every high risk eventuality, but for the patient who they treat most frequently. It is also very reassuring for patients. The missing information is the weighted duration across all six studies.

Reference:
1 SM Weisman, DY Graham. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. Archives of Internal Medicine 2002 162: 2197-2202.

Table 1: Outcomes in secondary prevention trials of aspirin

	Number of events		Percent of events			
	Aspirin	Placebo	Aspirin	Placebo	Relative risk (95% CI)	NNT/H
Total number	3127	3173				
Deaths	241	291	7.7	9.2	0.8 (0.7 to 0.99)	68 (35 to 1080)
All vascular events	607	788	19.4	24.8	0.7 (0.6 to 0.8)	18 (13 to 30)
Myocardial infarction	234	324	7.5	10.2	0.7 (0.6 to 0.8)	37 (25 to 75)
Stroke	193	231	6.2	7.3	0.8 (0.7 to 1.0)	90 (43 to 780)
GI bleeding	41	17	1.3	0.5	2.5 (1.4 to 4.7)	129 (80 to 330)

Figure 1: Crude pooled event rates of outcomes from six trials



Primary prevention with aspirin

A new review examines randomised trials of aspirin for at least one year to prevent cardiovascular disease events in patients without a history of cardiovascular disease [1].

Systematic review

There were two criteria, randomised trials of aspirin chemoprevention in patients without known cardiovascular disease, and systematic reviews, trials and observational studies examining haemorrhagic stroke and gastrointestinal bleeding secondary to aspirin use. The aim was to examine the balance of benefit and harm for aspirin in patients with different levels of risk for heart disease.

Results

Included were five randomised trials of aspirin on prevention of coronary heart disease, and nine articles on gastrointestinal bleeding or haemorrhagic stroke.

The five randomised trials had over 53,000 participants. The daily dose of aspirin was 500 mg in about 10% of these, and was 75 mg per day up to 325 mg every other day in most. Control was placebo or no treatment. Duration was 3.6 to 6.8 years. Most (80%) participants were middle-aged men.

Over about five years with control 2.4% had a coronary heart disease event, 0.6% died of a coronary heart disease event, 1.3% had a fatal or non-fatal stroke, and the all-cause mortality was 3.4%. Aspirin significantly reduced the number of coronary heart disease events (Figure 1) with a relative risk of 0.72 (95% CI 0.64 to 0.80). No other outcome was statistically different with aspirin. The number needed to treat with low dose aspirin for five years to prevent one coronary heart disease event that would not have happened with control was 190 (130 to 380).

Estimates for haemorrhagic stroke and gastrointestinal bleeding were taken from meta-analyses. The net impact of the benefits and harms of aspirin prophylaxis is shown in Table 1 for three different levels of five-year risk. At 3% and higher the benefits begin to outweigh the possible harm.

Comment

Previously it has been suggested that benefits of low dose aspirin outweigh the risks when the annual risk of a coronary event is 1%. This new analysis bears that out. The caution is that while coronary events are reduced, coronary death, strokes, and death from all causes were all unchanged by treatment.

Primary prevention and secondary prevention with aspirin are just different parts of a spectrum, as the similarity between Figure 1, and a L'Abbé plot of death from secondary prevention shows (Figure 2).

Reference:
1 M Hayden et al. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the US preventive services task force. Annals of Internal Medicine 2002 136: 161-172.

Figure 1: CHD events in primary prevention trials

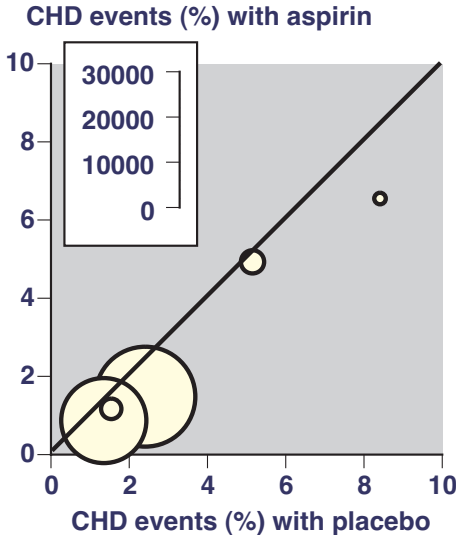


Figure 2: Deaths in secondary prevention trials for comparison

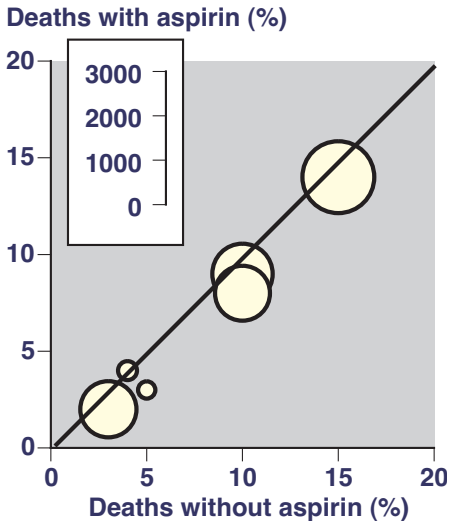


Table 1: Net impact of benefits and harms of aspirin prophylaxis at different levels of risk

Outcome	Estimated 5-year risk for CHD event at baseline		
	1 %	3 %	5 %
Effect on all-cause mortality	No change	No change	No change
CHD events avoided (per 1,000)	3	8	14
Ischaemic strokes avoided (per 1,000)	0	0	0
Haemorrhagic stokes caused (per 1,000)	**1**	**1**	**1**
Major gastrointestinal bleeding events (per 1,000)	**3**	**3**	**3**

Aspirin or anticoagulant in nonvalvular AF

Nonvalvular atrial fibrillation increases the risk of stroke by about four times. The issue is not so much whether to do anything, but rather what to do. Should treatment be with oral anticoagulants like warfarin, or with aspirin? Use of warfarin implies intermittent measurement of INR, and perhaps an increased risk of bleeding.

A number of reviews have addressed this, and generally they conclude that warfarin is more effective. A new meta-analysis has gone a step further, and obtained information on each individual patient [1].

Meta-analysis

There were six randomised trials with 4,052 patients. Patients were assigned to full-dose oral anticoagulant (target INR 2.5-4.0), or aspirin (75-325 mg/day) and (in some patients) low dose warfarin (median 2.0 mg/day). Low dose warfarin patients were included because there was no difference between them and because including such patients would be likely to minimise differences between treatments.

Patients were stratified according to risk of stroke:

- High risk – hypertension, diabetes, or prior cerebral ischaemia.
- Low risk – without these risk factors.
- Moderate risk – all other patients.

Six outcomes were sought:

- Ischaemic or haemorrhagic stroke
- Ischaemic stroke alone
- Haemorrhagic stroke alone (including subarachnoid and subdural haemorrhage)
- Aggregate cardiovascular events (ischaemic stroke, myocardial infarction, systemic embolism, or cardiovascular death)
- Major bleeding (including intracranial and systemic bleeding)
- All-cause death

Baseline features for each individual patient were provided by investigators. These included previous stroke or transient ischaemic attack, hypertension, congestive heart failure, diabetes and coronary artery disease. Mean follow up was for 1.9 years. Strokes were assessed by neuroimaging in 97% of cases.

Results

Oral anticoagulant was given to 1,939 patients and aspirin with or without low dose anticoagulant in 2,113. The groups were well matched at baseline after pooling data from six studies. Their mean age was 72 years and 60% were men. There was a high risk of stroke in 65%, moderate risk in 27% and low risk in 8%.

The main results are shown in Table 1. Oral anticoagulants were associated with reduced rates of all strokes, ischaemic strokes and cardiovascular events compared with aspirin. There was a significantly increased rate of major bleeding.

Across different subgoups the lower rate of ischaemic stroke and higher rate of major bleeds was consistent (age more or less than 75 years, men versus women, prior stroke or transient ischaemic attack, presence or absence of hypertension, congestive heart failure, diabetes, and different stroke risk).

Treating 1000 patients for one year with oral anticoagulants rather than aspirin would prevent 23 ischaemic strokes while causing nine additional major bleeding episodes.

Table 1: Outcomes in trials of aspirin versus oral anticoagulant for AF. Hazard ratios below 1 favour oral anticoagulant

Outcome	Events/100 patient-years		Hazard ratio (95% CI)
	Oral anticoagulant	Aspirin	
All stroke	**2.4**	**4.5**	**0.6 (0.4 to 0.7)**
Ischaemic stroke	**2.0**	**4.3**	**0.5 (0.4 to 0.6)**
Haemorrhagic stroke	0.5	0.3	1.8 (0.9 to 3.9)
All cardiovascular events	**5.5**	**7.8**	**0.7 (0.6 to 0.9)**
Myocardial infarction	0.7	1.0	0.6 (0.4 to 1.0)
Systemic emboli	0.2	0.3	0.7 (0.3 to 1.7)
Vascular death	3.1	3.2	1.0 (0.8 to 1.2)
Major bleeding	**2.2**	**1.3**	**1.7 (1.2 to 2.4)**
Lethal bleeding	0.4	0.2	2.2 (0.9 to 5.3)
All-cause death	4.9	5.2	0.9 (0.8 to 1.1)

Shaded rows show significant differences

Comment

This is a thorough review, and unless or until new trials are undertaken, it is likely to be the last and best word. The authors go to some length to explain any differences between this and previous meta-analyses, especially some differences in trial inclusion. Because of availability of data at the level of the individual patient rather than from published reports, several more trials could be included in the analysis.

They also explore how acceptable the magnitude of the effect might be to patients. They review studies that have looked at how patients view stroke. Patients have a strong aversion to stroke (the think it almost as bad as death), and would be willing to take warfarin even if the absolute risk reduction was 1% per year. Oral anticoagulants hit that 1% target.

A particular strength of the paper is that it is written to be read by people, not computers. A must-read paper.

Reference:

1 C van Walraven et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation. An individual patient meta-analysis. JAMA 2002 288: 2441-2448.

WHAT PATIENTS THINK

Much preventive prescribing is based on good evidence. Just like antiplatelets, for many interventions we have solid meta-analyses of good trials demonstrating clear statistical efficacy. We calculate NNTs or number of patients benefiting out of every 1,000 patients taking such-and-such medicine for three or five years. At a population level there is clear benefit.

What about the individual patient? What about their views concerning the amount of benefit that makes taking a medicine worthwhile for them? Even more, what about the balance of benefit and harm? ***Bandolier*** has long been aware that many people taking statins or anti-hypertensives believe that doing so prevents them having the heart attack or stroke they would have if they didn't take them. That's why they put up with, sometimes, quite awful adverse effects that have a big negative impact on the quality of their lives.

So a look at patient expectations [1] is a welcome breath of fresh air.

Study

Subjects were randomly selected from three groups:

1 Group 1 had just been discharged from the coronary care unit (CCU) with a diagnosis of myocardial infarction.
2 Group 2 had no recent history of myocardial infarction but were taking preventive cardiovascular drugs.
3 Group 3 had no known cardiovascular disease and were on no preventive cardiovascular drugs.

Out of 550 subjects, 308 (56%) agreed to participate, approximately 100 in each group. They were given an explanation of the study and a questionnaire. Subjects were asked to imagine that their blood cholesterol was higher than normal, putting them at an increased risk of heart attack in the next five years. They were told that a new, safe, drug was available which would reduce this risk, but would not benefit everyone. Some would not benefit because they would not have a heart attack anyway; some would not benefit because the drug was not strong enough to prevent a heart attack in them.

Table 1: Main results from three groups of patients - demographics and responses to questionnaires

Characteristic	Group 1 Just discharged from CCU	Group 2 On preventive drugs but no MI	Group 3 No preventive drugs, no MI
Mean age (years)	62	64	58
Percent men	76	53	45
Percent poor or very poor health	20	25	14
Smoker (%)	20	21	24
Against taking drugs	12	13	36
Want to know chance of benefiting (%)	79	72	84
Acceptable ARR reduction (median)	20%	20%	30%
Prolongation of life expected to be worth taking preventive medicine (month)	12	12	18
Percent prepared to take preventive drug with ≤5% chance of benefit over 5 years	32	29	21
Same, but if drug recommended by doctor	69	74	56

Table 2: Absolute risk reductions and approximate NNTs for a number of common interventions

Intervention	Duration (months)	Number of patients	Outcome	Untreated event rate (%)	Absolute risk reduction (%)	NNT
Pravastatin for secondary prevention	73	9014	Death	14.1	3.1	32
Pravastatin for primary prevention	59	6595	Coronary event	7.9	2.3	43
Ramipril in high risk patients	60	9297	Any MI	12.3	2.4	42
Antiplatelet post MI	27	20006	Vascular event	17	3.5	29
Hypertension DBP 80-109 mmHg	59	17354	Stroke	1.3	0.6	167
Warfarin in atrial fibrillation	22	571	Stroke	7.2	5.6	18

Subjects were asked to mark a visual analogue chart expressing benefit in a semilogarithmic fashion.

Results

There were some differences between the groups in demographics (Table 1), but about four out of five would want to know the chance of benefiting from treatment. Only a minority of patients would take a drug if they thought that they had a 5% chance or less of benefiting over five years (NNT about 20).

Half of the patients would take a drug if the chance of them benefiting over five years was 20% (NNT 5). Recommendation by their doctor increased the percentage of patients willing to take a preventive drug if the benefit was 5% or less over five years.

Comment

This is an interesting and imaginative paper that tells us what patients think. Half were happy to take a preventive drug if the hypothetical five year absolute risk reduction was 20%, or an NNT of 5. Table 2 shows some of the absolute risk reductions and NNTs from commonly used cardiovascular medicines. There is a clear discrepancy. Few preventive medicines for preventing heart attacks would seem to meet patient expectation.

And what is really important here is that in this paper, patients were told that the hypothetical treatment was safe. Safe has many connotations, but we know that many preventive treatments carry a significant burden of adverse effects. It would be interesting to repeat the study giving subjects a slightly harder task, choosing acceptable levels of benefit against different descriptions of likely harm. It is probable that the gap between expectation of benefit and delivery would grow even wider.

The saving grace in this study was the power of the doctor to advise. If their doctor recommended it, more than twice as many subjects would take the medicine. This, though, imposes a significant burden on doctors properly to inform their patients. Much less attention has been paid to how patients think about their own versus population benefit, and especially how the information is presented. An area where there is scope for more research, perhaps.

These results for what patients thought about heart attacks seem to be different from what patients thought about strokes. There appears to be a different attitude to stroke, which most seem to consider to be an outcome that is much more important to avoid.

It is interesting to speculate idly about a league table of patient wants and expectations concerning preventive interventions, matching intervention with patients' acceptance.

Reference:
1 PN Trewby et al. Are preventative drugs preventive enough? A study of patients' expectation of benefits from preventive drugs. Clinical Medicine 2002 2: 527-533.

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